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10/577,061	02/27/2007	Michel Cogne	1169-044	1063

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,061	COGNE ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/2/11*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-50,52-56 and 58-73* is/are pending in the application.

4a) Of the above claim(s) *60-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-50,52-56 and 59* is/are rejected.

7)☒ Claim(s) *58* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and remarks filed 2/2/11 are acknowledged. Claims 51, 57 have been canceled. Claims 36-50, 52, 53, 56, 58, 59 have been amended.

Claims 36-50, 52-56, 58-73 are pending, Claims 60-73 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions. Claims 36-50, 52-56, 58, 59 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims or persuasive argument will not be reiterated.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-50, 52 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 36-50, 52 are rejected under 35U.S.C. 112 first paragraph, because the specification as originally filed does not describe the invention as now claimed. The original disclosure fails to disclose a transgenic mouse that “produces no

immunoglobulins" as now claimed. The subject matter is now considered to be new matter.

The amended claim 36 add a new limitation "wherein said transgenic mouse produces no immunoglobulins".

MPEP 2163.02 teaches that "WHENEVER THE ISSUE ARISES, THE FUNDAMENTAL FACTUAL INQUIRY IS WHETHER A CLAIM DEFINES AN INVENTION THAT IS CLEARLY CONVEYED TO THOSE SKILLED IN THE ART AT THE TIME THE APPLICATION WAS FILED...IF A CLAIM IS AMENDED TO INCLUDE SUBJECT MATTER, LIMITATIONS, OR TERMINOLOGY NOT PRESENT IN THE APPLICATION AS FILED, INVOLVING A DEPARTURE FROM, ADDITION TO, OR DELETION FROM THE DISCLOSURE OF THE APPLICATION AS FILED, THE EXAMINER SHOULD CONCLUDE THAT THE CLAIMED SUBJECT MATTER IS NOT DESCRIBED IN THAT APPLICATION". MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added). In the instant case, the specification as originally filed describes, "*the inventors have constructed transgenic mouse lines which produce large quantities of humanized class IgA immunoglobulins (in the gram per liter range in mice)*". (Specification, paragraph 0024, for example). The specification is completely silent with respect to a "transgenic mouse produces no immunoglobulins" as now claimed. Thus, the amendment is a departure from or an addition to the disclosure of the application as filed, accordingly, it introduces new matter into the disclosure.

For reasons set forth above, the amendment filed 2/2/11 is objected to under 35 U.S.C. §132 because it introduces new matter into the disclosure. 35 U.S.C. §132 states that no amendment shall introduce new matter into the disclosure of the invention. Applicant is required to cancel the new matter in the reply to this Office Action. Alternatively, Applicant are invited to specifically point out where in the specification the support can be found for the amendment made to the disclosure.

To the extent that the claimed methods are not described in the instant disclosure, claims 36-50, 52 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-50, 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite because claim 36 recites "wherein said transgenic mouse produces chimeric immunoglobulins A" while also recites "said

transgenic mouse produces no immunoglobulins". It is unclear whether said mouse produces Igs or not, and hence the metes and bounds of the claims are uncertain.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 53-56, 58, 59 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Green et al.* (USP 7,547,817) in view of *Luby et al.* (J Exp Med 2001;193:159-68), for reasons of record and following.

Green teaches making a transgenic mouse for producing specific isotypes of human antibodies, wherein the transgenic mouse whose endogenous immunoglobulin gene was partially replaced with a human immunoglobulin heavy chain transgene including constant and variable regions and the exon encoding the CH3 domain and a membrane exon, a non-cognate switch region (e.g. the abstract and column 12) relative to the C_H gene (= deleting mouse Sμ, replacing it with a heterologous one from corresponding constant region). For example, *Green* teaches:

> In another embodiment, the human C.gamma.2 coding sequences, including all of the exons for the secreted and membrane-bound forms of the C.sub.H gene are replaced by another human C.sub.H gene. In this way, the human S.gamma.2 sequences control CSR from

> C.sub..mu. to the downstream C.sub.H gene. It is known that the hSg2 sequences are stable in yH1C while other human S sequences, some of which have longer tandem arrays of S repeats may be less stable. It is also known that CSR in transgenic mice with the human C.gamma.2 gene is efficient and generates high serum levels of human IgG2 and results in efficient production of fully human IgG2 mAbs. Thus, it may be preferable to retain the human S.gamma.2 with their favorable stability and in vivo response to antigen challenge while engineering CSR to occur to another isotype, e.g., either C.gamma.1 or C.gamma.4. To accomplish this, a vector with the following elements would be constructed: 5' homology located between human S.gamma.2 and the human C.gamma.2 coding exon 1, a human CH gene other than C.gamma.2, the mouse 3' enhancer, a yeast selectable marker, and 3' targeting homology in the YAC arm for example. (Emphasis added)

Here, the recited C.sub.H gene apparently includes Cα IgH locus. For example, when discussing the role of enhancers, *Green* mentioned the importance of a cluster of enhancers 3' of the Cα gene (column 13).

The exemplified transgenic mouse comprising a gene encoding human Ig kappa light chain (see e.g. claims 1, 2 and figure 1). *Green* teaches using the transgenic mouse for producing a [any] desired specific isotypes of human antibodies, wherein the endogenous IgH loci were inactivated (e.g. claim 3).

Green also teaches a targeting vector (e.g. the cited text *supra*) and ES cells comprising the vector, wherein the vector comprises the human IgH transgene composed of 66 VH, all the D and J elements, Cμ, Cδ, all regulatory elements, and all in germline configuration (column 10), which would include the heavy chain promoter. The vector also comprises intronic Eμ upstream, and palindrome hs3a/hs1,2/hs3b downstream (column 13), loxP sites and flanking (mouse) sequences of 5'- and 3'-targeting homology for homologous recombination (e.g. column 15). *Green* also teaches introducing the targeting vector into mouse ES cells (e.g. example 27), and breeding to homozygosis (e.g. example 29).

Green differs from instant claimed in that the inserted C_H gene operably linked to a non-cognate switch sequence whereas a preferred embodiment of instantly claimed transgenic animal does not contain a switch sequence. However, it is noted instant claims embrace a transgene comprising a non-cognate switch sequence.

Luby supplemented *Green* by establishing at the time of instant priority date, it was well known in the art that μ switch tandem repeats (Sμ) is important but not required for antibody class switch. *Luby* teaches a Sμ–deleted transgenic mouse made by homologous recombination, whose serum levels of antibodies showed slight reduction in IgG1 and IgG3, larger reduction in IgG2b, but no reduction in IgA (e.g. last

paragraph, page 161). The switch region Sμ in the targeting vector disclosed by *Luby* was deleted and replaced with a loxP recombinase recognition site downstream of Eμ and upstream of Cμ, providing a universal insertion site for insertion of any transgene of interest including Cα gene (figure 1). *Luby* concluded that sequences outside of the Sμ must be capable of directing class switch, while the absence of the Sμ may affect the efficiency of IgG production, but not the efficiency of IgA production.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the mouse taught by *Green* by replacing the mouse Sμ region with any constant region of interest using the construct as taught by either *Green* or *Luby* and particularly when the intended antibody to make is a human IgA and when the C_H is Cα as taught by *Green* in view of *Luby* to arrive at instantly claimed invention. Given the levels of the skilled as illustrated by *Green* in view of *Luby*, one would have had a reasonable expectation of success.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicant did not present argument concerning the targeting vector in the response to this rejection. The arguments regarding the transgenic mouse were moot because the claims are no longer rejected under this statue.

The prior rejection of Claim 58 under 35 U.S.C. 103(a) as being unpatentable over *Green et al.* (USP 7,547,817) in view of *Luby et al.* (J Exp Med 2001;193:159-68) as applied to claims 36-57, 59 above, further in view of GeneBank AC073553 (September 2002), is withdrawn in view of persuasive argument.

Claim Objections

Claim 58 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9 AM -7:00pm, Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI/
Primary Examiner, Art Unit 1633